

SRL 6109 (C-3115)
PATENTCC: Kears
4-5-01REMARKS

In view of the instant amendment and the remarks set out hereinbelow, it is respectfully submitted that the rejections under 35 U.S.C. §§102, 103 and 112 should be withdrawn and all claims found allowable over the prior art.

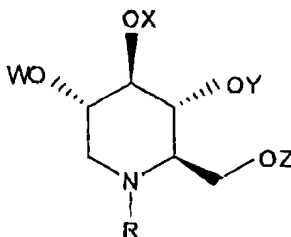
Claim Rejection under 35 U.S.C. §112

Claim 92 has been amended to correct the erroneous reference to "a method." This is believed to resolve the basis for the rejection of this claim under 35 U.S.C. §112.

Claim Rejections under 35 U.S.C. §102

Reconsideration is respectfully requested of the rejection of claims 1-46, 49-55, 59-115, and 118-124 under 35 U.S.C. §102 as anticipated by Partis et al. U.S. patent 5,144,037.

Claim 1 is directed to a method for treating a hepatitis infection in a mammal. The method comprises administering to the mammal an anti-hepatitis virus effective amount of at least one N-substituted 1,5,-dideoxy-1,5-imino-D-glucitol compound defined according to structural Formula I:



wherein R is selected from the group consisting of straight chain alkyl having a chain length of C₇ to C₂₀, branched chain alkyl

SRL 6109 (C-3115)
PATENT

having a chain length of C_3 to C_{20} in the main chain, alkoxyalkyl, arylalkyl, and cycloalkylalkyl, and W, X, Y and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl. Such compounds are commonly known as derivatives of 1-deoxynojirimycin ("DNJ").

Independent claims 9, 25, 33, 49, and 59 are also directed to methods for treatment of hepatitis virus in a mammal by administering a compound of Formula I. Independent claims 41, 58, and 59 call for the administration of both an N-substituted DNJ compound of Formula I and a second antiviral agent selected from among nucleosides, nucleotides, immunomodulators and immunostimulants.

Partis is directed to certain DNJ derivatives as compositions of matter. The reference reports that these derivatives are useful in the *in vitro* inhibition of visna virus, a form of lentivirus, that in turn is useful "as a model for human immunodeficiency virus (HIV)" (col. 6, lines 1-21). Thus, the reference is oriented toward HIV, not hepatitis infections. The Partis specification goes on to say that inhibitory activity can be demonstrated by the acylated DNJ derivatives against α - and β -glucosidases, and that the non-acylated derivatives also have effective inhibitory activity against visna virus, cytomegalovirus (CMV) and the α - and β -glucosidases (col. 6, lines 22-28). Further discussion of antiviral activity can be found at col. 39, lines 24-47. Partis concludes that the "antiviral agents described herein can be used for administration to a mammalian host infected with a lentivirus, e.g., visna virus or the human immunodeficiency virus."

Nowhere do Partis et al. disclose or suggest the instantly claimed method of administering a DNJ derivative for treatment of infectious hepatitis. Since Applicants' claims are directed to "treating a hepatitis infection in a mammal," they call for

SRL 6109 (C-3115)
PATENT

administration of a DNJ derivative to a host that is suffering from or exposed to such an infection. Partis do not disclose or suggest treatment of a host suffering from any hepatitis infection. Moreover, the exemplary disclosure of Partis describes only *in vitro* experimentation. Thus, there is no basis for any conclusion that the method of claims 1-46, 49-55 or 59-76 is either expressly or inherently disclosed by Partis. These claims clearly meet the novelty standard of 35 U.S.C. §102.

Novelty of method claims 41-46, 49-55 and 59 is further established by the required administration of a second antiviral agent selected from among nucleosides, nucleotides, immunomodulators and immunostimulants. Partis contains no disclosure or suggestion of such combination.

Each of independent claims 77, 85, 93, 101 and 118 is directed to a pharmaceutical composition that contains an antiviral effective amount of at least one N-substituted DNJ compound of Formula I, together with a pharmaceutically acceptable carrier, excipient or diluent. Independent claims 109 and 118 further require the presence of another antiviral agent selected from among nucleosides, nucleotides, immunomodulators and immunostimulants. The claimed compositions are useful in the treatment of hepatitis infections.

Partis does not provide an enabling disclosure of any pharmaceutical composition containing a pharmaceutically acceptable carrier, excipient or diluent. The only quantitative information in the application relates to concentrations of DNJ compounds used in an *in vitro* plaque reduction assay. No quantitative information is provided regarding the amount of active ingredient content that should be included in any pharmaceutical composition or the dosage to be administered. The reference contains only a general statement to the effect that the antiviral agents described are preferably administered in

SRL 6109 (C-3115)
PATENT

formulations with pharmaceutically acceptable diluents and carriers.

Moreover, note that only two of the nearly 70 exemplary compounds described by Partis, i.e., N-nonyl DNJ (Example 13) and N-nonyl DNJ tetraacetate (Example 14), fall within the scope of Formula I as set forth in the claims of the instant application; and of the 53 compounds listed in columns 2 and 3 of Partis, only the N-nonyl DNJ tetraacetate corresponds to Formula I. While the Office action refers to Partis et al's disclosure of N-butyl, pentyl, hexyl, aroyl and acyl substituted DNJs, it is respectfully noted that none of compounds having these latter N-substituents is within the scope of Formula I as set forth in any of claims 77-115 or 118-124. Only the two N-nonyl derivatives are encompassed by this formula.

Of the two N-nonyl compounds which Partis et al. disclose, only N-nonyl DNJ tetraacetate (Example 14) was tested in any manner for its efficacy as an antiviral agent of any nature. As described in Example 43, compounds were tested by *in vitro* plaque reduction assay against visna virus in sheep choroid plexus cells. Per this *in vitro* assay, N-nonyl DNJ tetraacetate was reported only as "Toxic." No indication of efficacy is given. The disclosure of only two relevant compounds, one entirely untested and the other reported as Toxic, cannot be considered an enabling disclosure of the composition of claims 77-115 or 118-124. Accordingly, these claims are respectfully submitted as meeting the test of novelty.

Claims 109-115 and 118-124 further distinguish Partis by requiring the presence of a second antiviral agent comprising a nucleoside, nucleotide, immunomodulator or immunostimulant.

SRL 6109 (C-3115)
PATENT

Reconsideration is further requested of the rejection of claims 47, 56, 116, 125 and 134 under 35 U.S.C. §102 as anticipated by Schinazi et al. U.S. patent 5,703,058.

All of the rejected composition claims require the presence of an N-substituted DNJ compound of Formula I, and all the rejected method claims call for the administration of an N-substituted DNJ compound which also corresponds to this Formula. As noted in the Office action, Schinazi discloses the treatment of hepatitis B using various nucleoside or nucleotide derivatives of 2,3-dideoxy-3'-thiacytidine (3TC), but there is no disclosure whatsoever of any composition comprising any DNJ derivative, nor the administration of any DNJ derivative for any purpose. Accordingly, none of the methods of claims 47 and 56, and none of the pharmaceutical compositions of claims 116, 125 and 134, is anticipated by Schinazi under 35 U.S.C. §102.

Cited in the specification of the instant application is WO 95/19172 which describes the treatment of hepatitis B with N-alkyl DNJ compounds wherein the alkyl group contains between three and six carbon atoms. The specification also cites Block, T.M., *Proc. Natl. Acad. Sci. USA* (1994) 91:2235-2239; and Ganem, B. *Chemtracts: Organic Chemistry* (1994) 7(2), 106-107. However, none of these references describes or suggests the treatment of any hepatitis infection with a C₇ to C₂₀ N-alkyl DNJ compound.

It is therefore respectfully requested that the novelty rejections be withdrawn.

Priority of Monotherapy and Combination Therapy Inventions

Applicants respectfully acknowledge the principles discussed in the first paragraph of page 4 of the Office action, relating to common ownership. For purposes of this record, it should be assumed that there is a difference in ownership between the

SRL 6109 (C-3115)
PATENT

inventions directed to "monotherapy," i.e., claims which require administration of an N-substituted DNJ compound but not a second antiviral agent, and claims directed to "combination therapy," i.e., claims that are directed to the administration of both an N-substituted DNJ compound and a second antiviral agent selected from among nucleosides, nucleotides, immunomodulators and immunostimulants. Inventors in the monotherapy methods and compositions are Richard A. Mueller and Martin L. Bryant. Other inventors contributed to combination therapy methods and compositions.

The question of priority between the monotherapy and combination therapy inventions is complex; and neither Applicants nor their undersigned attorney have undertaken an investigation adequate to resolve the issue. However, it is believed that neither of these inventions is obvious from the other, rendering the resolution of priority moot. Thus, the invention in combination therapy is clearly not obvious from the invention in monotherapy. The invention in combination therapy would not have been obvious from the invention in monotherapy because, as explained below, there is no basis in the references or the skill of the art creating any motivation to combine N-substituted DNJ compounds with nucleosides, nucleotides, immunomodulators or immunostimulants for treatment of hepatitis infections. On the other hand, the invention in monotherapy would not have been obvious from the invention in combination therapy, because the inventors who discovered the latter method would have and did emphasize the desirability and importance of the second antiviral agent, effectively teaching away from monotherapy.

Claim Rejections under 35 U.S.C. §103

Reconsideration is respectfully requested of the rejection of claims 48, 57, 58, 117, 127, and 135-149 as unpatentable over Partis et al. in view of Schinazi et al. under 35 U.S.C. §103(a).

SRL 6109 (C-3115)
PATENT

Each of claims 48, 57, and 58 is directed to combination therapy in which a hepatitis infection is treated by administration of both an N-substituted DNJ compound of Formula I and a second antiviral selected from among nucleosides, nucleotides, immunomodulators and immunostimulants. Claims 117, 127, and 135-149 are directed to pharmaceutical compositions containing both an N-substituted DNJ compound of Formula I and one or more of the aforesaid second antiviral agents.

Contrary to the apparent premise of the §103 rejection, Partis et al. fail to disclose or suggest the administration of any DNJ derivative for treatment of a hepatitis infection. Schinazi, on the other hand, contains no disclosure of any DNJ compound or use thereof. Accordingly, it is respectfully suggested that no basis exists for combining these references, certainly not in any way relevant to the instantly claimed invention.

More particularly, there is no basis in Partis et al. or Schninazi for combining an N-substituted DNJ compound and a nucleoside, nucleotide, immunomodulator or immunostimulant for treatment of infectious hepatitis. The references do not suggest such combination, provide any motivation to make such combination, nor provide any reasonable basis for expectation that the combination would offer any benefit or advantage.

Partis does not suggest combining N-substituted DNJ compounds with any other antiviral for treatment of any condition. Partis proposes administration of DNJ derivatives alone, and then only for HIV, visna virus, or cytomegalovirus (CMV). Partis reports that the DNJ derivatives inhibit α - and β -glucosidases, but does not suggest such derivatives would have any use in treatment of infectious hepatitis. Schinazi describes administration of certain nucleoside and nucleotides, but does not suggest using an N-substituted DNJ compound at all. The

SRL 6109 (C-3115)
PATENT

Schinazi reference includes a catchall afterthought to the effect that the nucleosides and nucleotides disclosed "can also be mixed with other active materials that do not impair the desired action, such as antibiotics, antifungals, antiinflammatories, or other antivirals, including other nucleoside anti-HIV compounds" (emphasis supplied). However, this appears to be merely a negation of contraindications, not an affirmative recommendation to combine nucleoside antivirals with any other antiviral, much less a suggestion that any advantage would accrue therefrom. Contrary to suggestion at page 5 of the Office action, col. 20 of Schinazi offers absolutely no intimation of any enhanced effect of mixing thiacytidine compounds with other antiviral, anti-HIV, or anti-HBV agents for any purpose. Nor can Schinazi remotely be construed as suggesting that nucleosides be combined with N-substituted DNJ compounds selected to fall within the scope of Formula I.

Therefore, it is respectfully submitted that motivation to combine N-substituted DNJ compounds with nucleosides or nucleotides cannot be found in the catchall afterthought of Schinazi, col. 20. Schinazi does not identify any particular antiviral with which his disclosed nucleosides or nucleotides can safely be mixed; and he suggests neither "increased effectiveness" nor other advantage from such "mixing." It is respectfully submitted that perception by one skilled in the art of any purpose in combining N-substituted DNJ compounds with the nucleoside or nucleotides of Schinazi would be entirely an exercise in hindsight.

Although it has been theorized that the efficacy of the instantly claimed method may be based in part on inhibition of glucosidases, the passing mention in Partis of α - and β -glucosidase inhibition would not have provided any basis for predicting efficacy of any N-substituted DNJ compound against hepatitis infections. The differences between hepatitis viruses

SRL 6109 (C-3115)
PATENT

and Lentiviruses are too substantial. Assuming *arguendo* that one skilled in the art had perceived the potential effectiveness of the Formula I DNJ derivatives based on glucosidase inhibition, such perception could scarcely have led to combining any DNJ derivative with nucleosides, which work in an entirely unrelated manner, i.e., by phosphorylation and incorporation into DNA. As explained by Schinazi:

"After cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3'-hydroxyl group." (col. 1, lines 29-34)

Only by hindsight could a skilled worker art find a basis for combining nucleosides that work like this with compounds of unrelated structure which happen to inhibit glucosidases.

Accordingly, it is respectfully submitted that there is no basis for *prima facie* obviousness of the method of claims 48, 57 or 58, or of the pharmaceutical compositions of claims 117, 127 or 135-149. The claimed methods and compositions are respectfully submitted as patentable over these references under 35 U.S.C. §103(a).

On similar grounds, it is respectfully submitted that there is no proper basis for rejection of claims to the combined administration of N-substituted DNJ compounds and other antiviral agents over Schinazi and the instantly claimed invention in monotherapy (assuming for this purpose, and this purpose only, the invention in monotherapy was prior to the invention in combination therapy).

Inasmuch as the disclosures of WO 95/19172, Block et al. and Ganem are limited to the treatment of hepatitis infections using

SRL 6109 (C-3115)
PATENT

C₃ to C₆ N-alkyl DNJ derivatives, these references cannot be construed as suggesting either monotherapy or combination therapy using the C₇ to C₂₀ N-alkyl DNJ compounds that are called for in the claims of the instant application. In any event, the postulated modes of action of the glucosidase-inhibiting DNJ compounds and the DNA chain-terminating nucleosides is so radically different that one skilled in the art would have seen no basis for their combination.

No Stated Ground of Rejection of Claims 126 or 128-133

Since the action states no ground of rejection of any of composition claims 126 or 128-133, it appears to Applicants that the Examiner may have intended to find these claims allowable. In any event, it is respectfully submitted that each of these claims is patentable over the art of record.

Claim 126 calls specifically for a composition comprising the combination of N-(n-nonyl) DNJ, N-(n-nonyl) DNJ tetrabutyrates, a pharmaceutically acceptable salt thereof, or mixtures thereof, with (-)-(2'-deoxy-3'-thiocytidine-5'-triphosphate. Claims 128-133 are directed to compositions comprising quantitative amounts of an N-substituted DNJ compound of Formula I in combination with a nucleoside or nucleotide antiviral agent.

It is respectfully submitted that there is no basis in the references for establishing either a lack of novelty or obviousness of the compositions of any of claims 126 or 128-133.

Copending Application

A U.S. national application, S.N. 09/355,446, claiming the priority of WO 98/35,685, is pending in the Patent and Trademark Office. The '446 application includes claims which overlap the

SRL 6109 (C-3115)
PATENT

combination therapy claims pending herein. The '446 application contains no monotherapy claims.

An Office action was issued December 15, 2000 in Ser. No. 09/355,446, rejecting all claims under 35 U.S.C. §103 as unpatentable over WO 95/06061. A copy of that action is enclosed. A response to the action in Ser. No 09/355,446 is being filed today.

It is respectfully submitted that the claims of the instant application are patentable over WO 95/06061, which is directed to the administration of certain urea-containing hydroxyethylamine protease inhibitors for treatment of HIV infections. Thus, the principal thrust of this reference is entirely unrelated to the instantly claimed invention which contemplates treatment of infectious hepatitis, not HIV, by administration of a DNJ derivative, not a urea-containing hydroxyethylamine protease inhibitor.

In addition to its primary teaching, '06061 discloses the administration of combinations of the urea-containing hydroxyethylamine protease inhibitor with two or three other antiviral agents which are effective against HIV. Other antiviral agents are described as including various nucleoside analogs, nonnucleoside reverse transcriptase inhibitors, tat antagonists and glycosidase inhibitors (p. 64, line 2). Among the competitive nucleoside analogs that can be used in the combination with a protease inhibitor for treatment of HIV are AZT, DDI, DDC, 3TC, D4T, and PMEA (p. 65, lines 27-29). Examples of the glycosidase inhibitors which can be used with a protease inhibitor are N-butyl DNJ and N-butyl DNJ perbutyrate (p. 66, lines 15 to 19).

Whatever the reference may teach about combining a urea-containing hydroxyethylamine with either a nucleoside, a

SRL 6109 (C-3115)
PATENT

nonnucleoside reverse transcriptase inhibitor, or a glycosidase inhibitor, or even combinations of these, for treatment of HIV, there is no teaching or suggestion of the particular combination of a DNJ derivative and a nucleoside for any purpose. Only hindsight could lead one skilled in the art to select the combination of a nucleoside and a glycosidase inhibitor, further selecting a DNJ derivative as the latter component.

But assuming *arguendo* that one skilled in the art might select some combination of protease inhibitor, nucleoside, and DNJ derivative for treatment of HIV, there is no suggestion in the reference of administering this particular combination for treatment of hepatitis infections.

The Examiner in the '446 application cites the passage at p. 66, lines 24 to 34 which states that the urea-containing hydroxyethylamine protease inhibitors of the -06061 publication are contemplated for treatment of a substantial list of disparate viruses, including hepadnaviruses. However, there is no suggestion in this passage that combinations of any DNJ derivative and nucleoside compound be administered for treatment of hepadnaviruses.

SRL 6109 (C-3115)
PATENTVERSION WITH MARKINGS TO SHOW CHANGES MADE

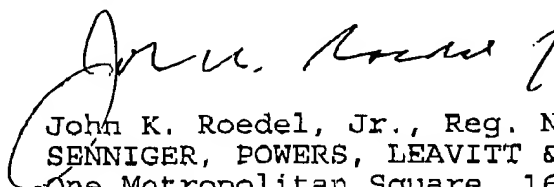
92. (once amended) The [method] pharmaceutical composition of claim 85, wherein said pharmaceutically acceptable salt is selected from the group consisting of acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate, and undecanoate.

SRL 6109 (C-3115)
PATENT

CONCLUSION

In view of the foregoing, it is respectfully submitted that all claims now pending the application fully satisfy the requirements of 35 U.S.C. §§102, 103 and 112, and that the instant application is in condition for allowance. Favorable reconsideration and early allowance of all claims are respectfully solicited.

Respectfully submitted,



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